Organic LETTERS

Letter

pubs.acs.org/OrgLett

Copper-Catalyzed Hydroamination of Alkynes with Aliphatic Amines: Regioselective Access to (1*E*,3*E*)-1,4-Disubstituted-1,3-dienes

Janet Bahri,[†,‡] Bassem Jamoussi,[‡] Arie van Der Lee,[§] Marc Taillefer,*[,†] and Florian Monnier*[,†]

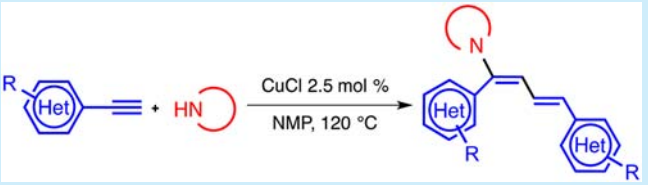
[†]Ecole Nationale Supérieure de Chimie de Montpellier, Institut Charles Gerhardt, CNRS UMR 5253, AM2N, 8 rue de l'Ecole Normale, 34296 Montpellier Cedex 05, France

[‡]Laboratoire de Chimie, Institut Supérieur d'Education et de Formation Continue, 43 Rue de la Liberté, 2019, Le Bardo, Tunisie

[§]IEM Université Montpellier, 2 Case courrier 047 Place Eugène Bataillon, 34095 Montpellier cedex 5, France

Supporting Information

ABSTRACT: Copper-catalyzed hydroamination of aromatic or heteroaromatic alkynes with cyclic secondary aliphatic amines undergoes generation of an enamine-type intermediate. The latter is transformed in situ via a coupling reaction with a second molecule of alkyne to afford regioselectively (1*E*,3*E*)-1,4-disubstituted-1,3-dienes with the formation of C−N, C−C, and C−H bonds.



The development of clean syntheses with respect to atom economy by the selective combination of several molecules into only one product is receiving increasing interest.[1] Molecular catalysts are currently playing a key role in such innovative synthetic methods.[2] Transition metal catalysts allow the synthesis of complex targeted molecules through highly simplified routes involving the combination of simple and readily available substrates and the formation of several consecutive bonds with high selectivity. Alkyne and amine molecules emerged as attractive substrates because the addition of N-nucleophiles (N−H) to triple C−C bonds affords a high-valued molecule via a hydroamination-type reaction with the formation of C−N and C−H bonds.[3] This type of reaction is a major goal for chemists to obtain functionalized unsaturated amines via a 100% atom-economical pathway.[4] Recently, hydroamination mediated by acids, bases, alkaline earth metals, lanthanides, and actinides has been performed.[5] Transition-metal-catalyzed hydroamination of alkynes has also been developed in recent years,[6] notably with Ag, Au, Pt, Pd, Rh, Ir, and Ru catalysts. Unlike these expensive metal sources, cheaper and more sustainable metals such as copper have received limited attention.[7] Thus, most of the Cu-catalyzed hydroamination reactions have been described in an intramolecular fashion to afford N-heterocycles.[8] Only a few reports have been developed for intermolecular reactions. Most of them make use of heterogeneous copper-supported catalysts and are limited to the formation of imines from primary amines.[9] Only one example of a simple hydroamination of terminal alkynes with anilines affording the corresponding imines has been described (with CuCl used in homogeneous conditions).[7d] The principal limitation of these copper catalysts is the exclusive use of primary amines as substrates. Thus, there is a need to discover a novel and simple system to extend the copper-catalyzed hydroamination of alkynes to secondary amines to produce enamines and dieneamines.

As part of our studies on copper-catalyzed cross-coupling reactions,[10] herein we report a one-pot regioselective access to (1*E*,3*E*)-1,4-disubstitued-1,3-dienes via a sequential formation of C−N, C−H and C−C bonds relative to a hydroamination-type intermediate. The synthesis of this original class of complex molecules is catalyzed by a simple copper salt (CuCl) without any additive ligands, and is made from the reaction of 2 equiv of terminal arylacetylenes with cyclic secondary aliphatic amines. It is noteworthy that dienamine chemistry is a valuable tool in organic chemistry, especially in bioactive molecules, natural products, and organocatalysis.[11]

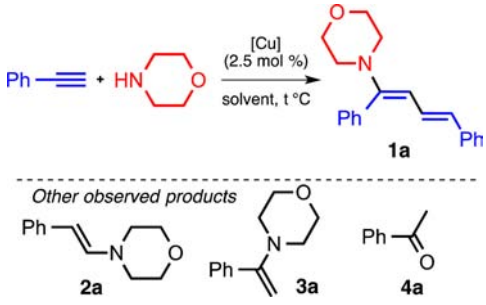
Initial tests were done on phenylacetylene (2 mmol) and morpholine (5 mmol) as model substrates with a ligandless copper catalyst (2.5 mol % of Cu(0), Cu(I), or Cu(II) catalysts) in NMP to observe the reactivity of this system (Table 1). First, we observed a mixture of classical hydroamination products such as enamine coming from the Markovnikov and anti-Markovnikov addition of morpholine, respectively **2a** and **3a** (only observed by GC-MS due to a rapid degradation), and a degradation product **4a** coming from hydrolysis of **3a** (Table 1, entries 1−8). In all cases, molecules **2a**, **3a**, and **4a** were unselectively observed in low to fair yields. Surprisingly, whatever the copper source, we also observed an unexpected product **1a** in moderate to large amounts. After purification and isolation of the latter, we identified **1a** as 4-((1*E*,3*E*)-1,4-diphenylbuta-1,3-dien-1-yl)morpholine. We rapidly thought that the formation of this compound was synthetically interesting as, to the best of our knowledge, there is no precedent in the literature of this kind of high-valued molecule synthesis.[11]

Following this initial success, we decided to focus on the optimization of the reaction conditions to afford **1a** in the most

Received: January 19, 2015
Published: February 23, 2015

DOI: 10.1021/acs.orglett.5b00177
Org. Lett. 2015, 17, 1224−1227

Table 1. Hydroamination of Phenylacetylene: Parametric Study[a,b]



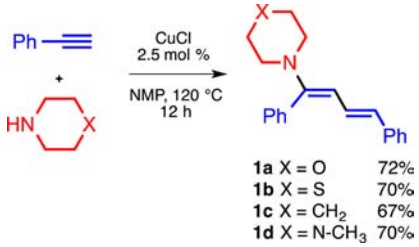
entry	solvent	[Cu]	*t*, °C	1a	2a	3a	4a
1	NMP	CuBr	120	53	20	10	17
2	NMP	CuI	120	55	18	12	15
3	NMP	Cu_2O	120	30	5	5	10
4	NMP	CuCN	120	12	10	7	12
5	NMP	CuF_2	120	40	13	10	10
6	NMP	CuO	120	10	5	5	9
7	NMP	$CuBr_2$	120	25	5	4	11
8	**NMP**	**CuCl**	**120**	**75**	**4**	**6**	**15**
9	DMA	CuCl	120	60	10	10	20
10	DMF	CuCl	120	10	70	4	16
11	DMSO	CuCl	120	12	65	5	18
12	dioxane	CuCl	120	0	60	5	35
13	HMPA	CuCl	120	0	65	5	10
14	CH_3CN	CuCl	120	0	20	7	10
15	toluene	CuCl	120	0	45	5	11
16	NMP	$Cu(acac)_2$	120	37	7	5	10
17	NMP	CuCl	25	0	5	0	0
18	NMP	CuCl	90	12	5	3	5
19	NMP	CuCl	μW	14	35	45	6
20	NMP	–	120	0	0	0	0

[a]Conditions: phenylacetylene (2 mmol), morpholine (5 mmol), CuCl (0,05 mmol), 2 mL of solvent, 12 h of reaction. [b]GC Yields with 1,3,5-trimethoxybenzene as internal standard.

selective manner. As resumed in Table 1, we found that CuCl was the most efficient copper source (Table 1, entries 1−8) associated with the NMP as solvent (Table 1, entries 8−15) for the generation of **1a** in 75% NMR yield (entry 8). We also showed that thermal activation at 120 °C is needed for the synthesis of **1a** as neither rt nor 90 °C allow good formation of the desired product. Activation by microwaves is also unsuitable for this transformation (Table 1, entry 19). It is noteworthy that none of the products **1a**−**4a** were observed in the absence of any copper sources (entry 20). We also observed an important decrease in yields and selectivities if we add <2.5 equiv of morpholine or <2.5 mol % of CuCl. At this stage of the investigation, we were able to selectively isolate 75% of **1a** starting from 1 mmol of phenylacetylene (with a second addition after 2 h of reaction at 120 °C) and 2.5 mmol of morpholine catalyzed by 2.5 mol % of CuCl in NMP at 120 °C over 12 h.[12]

On the basis of these results, we wished to demonstrate further the efficiency and functional group tolerance of this novel reaction by varying substitution on aryl acetylenes and amines. First, we were able to apply our method to various cyclic secondary amines (Scheme 1).[13] Phenylacetylene easily reacted under optimized conditions with morpholine, thiomorpholine, piperidine, and 4-methylpiperazine to afford the

Scheme 1. Reaction Scope with Various Six-Membered Ring Amines (Isolated Yields)



corresponding target dienes **1a**, **1b**, **1c**, and **1d** respectively in 72%, 70%, 67%, and 70% isolated yields.

Furthermore, we could isolate crystals of **1c** that were suitable for X-ray structure analysis (CCDC 1029186) (Figure 1). The structure revealed the relative spatial position of the

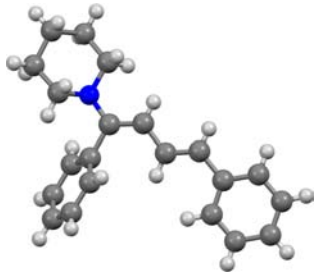
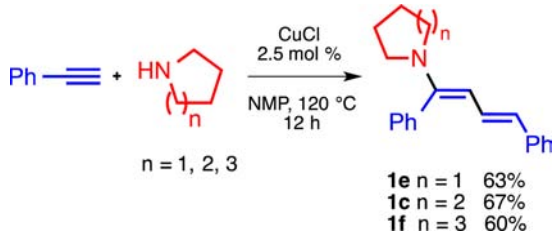


Figure 1. ORTEP drawing of the molecular structure of **1c** (nitrogen atom in blue).

piperidine substituent on the first double bond. The structure also reveals the stereochemistry of both double bonds (e.g., 1*E*,3*E*) and the *trans* junction between them. All these observations were correlated by NMR experiments and the different coupling constants observed in all the ^{1}H NMR spectra of 1,4-disubstituted-1,3-dienes **1a**−**1t**.

We also demonstrated that this original method is tolerant of cyclic amines of various sizes and different substitutions. Thus, under classical conditions, it was shown that the reaction proceeds with very good selectivities starting from pyrrolidine, piperidine, and azepane, the corresponding products **1e**, **1c**, and **1f** being obtained respectively in 63%, 67%, and 60% yields (Scheme 2).

Scheme 2. Scope of the Reaction with Differents Sizes of Cyclic Amines (Isolated Yields)

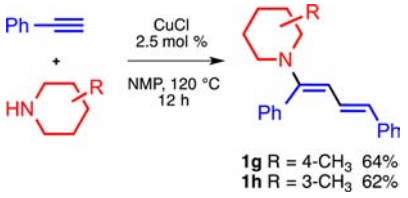


We also noted that substitutions on the piperidine partner did not affect the reactivity, as we isolated the corresponding dienes **1g** and **1h** in 64% and 62% yields (Scheme 3).

Then, we decided to investigate the scope of this hydroamination process by evaluating a series of various electronically varied arylacetylenes under one set of optimized

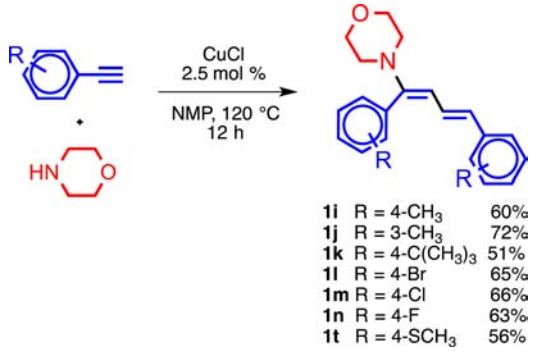
DOI: 10.1021/acs.orglett.5b00177
Org. Lett. 2015, 17, 1224−1227

Scheme 3. Examples from Substituted Piperidines (Isolated Yields)



conditions (Scheme 4). Moderate to good yields were obtained with terminal alkynes substituted on the aryl ring by methyl,

Scheme 4. Reaction Scope with Various Substituted Arylacetylenes (Isolated Yields)



tert-butyl, and thiomethyl groups (Scheme 4, products **1i**–**1k** and **1t**). Additionally, we also tested para-halogenated aromatic alkynes, and corresponding dienes were isolated in good yields (for R = Br: 65% of **1l**, for R = Cl: 66% of **1m**, and for R = F: 63% of **1n**).

Finally, we showed that this methodology is tolerant and efficient if hetero- and polyaromatic alkynes are used as starting materials (Figure 2). Under optimized conditions, we were able

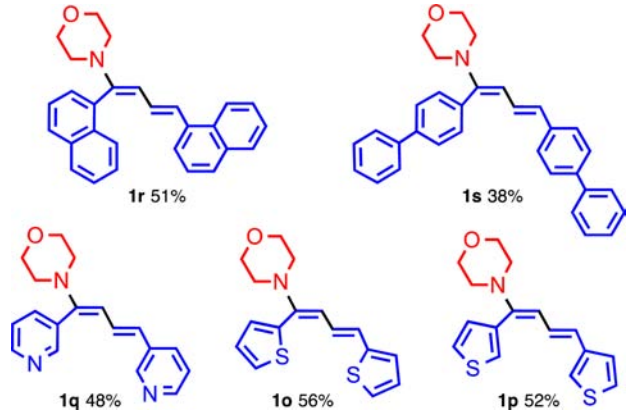


Figure 2. Reaction scope with various aromatic and heteroaromatic alkynes (isolated yields).

to isolate **1o**, **1p**, **1q**, **1r**, and **1s** starting respectively from 2-thienyl, 3-thienyl-, 3-pyridyl-, 2-naphthyl-, and 4-biphenyl-acetylene in good to moderate yields. In the case of biphenylacetylene, the moderate yield of **1s** could be explained by the important steric hindrance.

Although we do not have any proof of the mechanism of this transformation, we think the first step is generation via a hydroamination reaction of an enamine-type intermediate coordinated to copper, the latter being able to activate (coordination/insertion) a second molecule of alkyne before the formation and release of the dieneamine. Further investigations on the mechanism of this reaction are in progress.

In summary, a novel type of functionalization of alkynes with cyclic secondary amines has been developed. Starting from these very accessible and simple substrates, a low catalytic amount of CuCl allows regioselective one-pot access to (1*E*,3*E*)-1,4-disubstitued-1,3-dienes. This reaction proceeds via a sequential formation of C–N and C–C bonds relative to a hydroamination-type intermediate. This original reaction allows simple and cheap access to dienamines which are valuable tools in bioactive-natural synthesis and in organo-catalysis.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and characterization data for all new compounds, and X-ray structural data for **1c** (CCDC 1029186). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: marc.taillefer@enscm.fr.
*E-mail: florian.monnier@enscm.fr.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Authors thank CNRS, Proclean and Région Languedoc-Roussillon for support and Martin Pichette-Drapeau (Université Laval, Canada) for proofreading this manuscript.

■ REFERENCES

(1) Li, C. J.; Trost, B. M. *Proc. Natl. Acad. Sci. U.S.A.* **2008**, *105*, 13197.
(2) Beller, M.; Bolm, C. *Transitions Metals for organic Synthesis: Building Blocks and Fine Chemicals*, 2nd revised and enlarged ed.; Wiley-VCH: 2008.
(3) (a) Nishina, N.; Yamamoto, Y. *Topics in Organometallic Chemistry*; Springer: 2013; Vol. *43*, p 115. (b) Reznichenko, A. L.; Hultzsch, K. C. *Topics in Organometallic Chemistry*; Springer: 2013; Vol. *43*, p 51.
(4) Nobis, M.; Driesen-Hölscher, B. *Angew. Chem., Int. Ed.* **2001**, *40*, 3983.
(5) (a) Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795. (b) Hannedouche, J.; Shulz, E. *Chem.—Eur. J.* **2013**, *19*, 4972. (c) Schafer, L. L.; Yim, J. C. H.; Zonson, N. *Metal-catalyzed Cross-coupling Reactions and More*, 1st ed.; Wiley-VCH: 2014; p 1135.
(6) (a) Severin, R.; Doye, S. *Chem. Soc. Rev.* **2007**, *36*, 1407–1420. (b) Lavallo, V.; Frey, G. D.; Donnadieu, B.; Soleilhavoup, M.; Bertrand, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 5224. (c) Kinjo, R.; Donnadieu, B.; Bertrand, G. *Angew. Chem., Int. Ed.* **2011**, *50*, 5560. (d) Sakai, K.; Kochi, T.; Kakiuchi, F. *Org. Lett.* **2011**, *13*, 3928. (e) Patil, N. T.; Kavthe, R. D.; Shinde, V. S. *Tetrahedron* **2012**, *68*, 8709. (f) Yim, J. C. H.; Schafer, L. L. *Eur. J. Org. Chem.* **2014**, 6825. (g) Alamsetti, S. K.; Person, A. K A.; Bäckvall, J.-E. *Org. Lett.* **2014**, *16*, 1434. (h) Su, Y.; Lu, M.; Dong, B.; Chen, H.; Shi, X. *Adv. Synth. Catal.* **2014**, *356*, 692.

DOI: 10.1021/acs.orglett.5b00177
Org. Lett. 2015, 17, 1224–1227

(7) (a) Zhou, L.; Bohle, D. S.; Jiang, H. F.; Li, C. J. *Synlett* **2009**, 937. (b) Zheng, Q.; Hua, R. *Tetrahedron Lett.* **2010**, *51*, 4512. (c) Han, J.; Xu, B.; Hammond, G. B. *Org. Lett.* **2011**, *13*, 3450. (d) Robbins, D. W.; Hartwig, J. H. *Science* **2011**, *333*, 1423. (e) Gupta, S.; Agarwal, P. K.; Saifuddin, S.; Kundu, B. *Tetrahedron Lett.* **2011**, *52*, 5752. (f) Verma, A. K.; Jha, R. R.; Chaudary, I.; Tiwari, R. K.; Reddy, K. S. K.; Danodia, A. *J. Org. Chem.* **2012**, *77*, 8191.

(8) (a) Müller, T. E.; Grosche, M.; Herdtweck, E.; Pleier, A. K.; Walter, E.; Yan, Y. K. *Organometallics* **2000**, *19*, 170. (b) Krasnova, L. B.; Hein, J. E.; Fokin, V. V. *J. Org. Chem.* **2010**, *75*, 8662. (c) Tokimizu, Y.; Ohta, Y.; Chiba, H.; Oishi, S.; Fuji, N.; Ohno, H. *Tetrahedron* **2011**, *67*, 5168. (d) Chen, D. S.; Zhang, M. M.; Li, Y. L.; Liu, Y.; Wang, X. S. *Tetrahedron* **2014**, *70*, 2889. (e) Pouy, M. J.; Delp, S. A.; Uddin, J.; Ramdeen, V. M.; Cochrane, N. A.; Fortman, G. C.; Gunnoe, T. B.; Cundari, T. R.; Sabat, M.; Myers, W. H. *ACS Catal.* **2012**, *2*, 2182.

(9) (a) Joseph, T.; Shanbhag, G. V.; Halligudi, S. B. *J. Mol. Catal. A.: Chem.* **2005**, *236*, 139. (b) Shanbhag, G. V.; Kumber, S. M.; Joseph, T.; Halligudi, S. B. *Tetrahedron Lett.* **2006**, *47*, 141. (c) Shanbhag, G. V.; Joseph, T.; Halligudi, S. B. *J. Catal.* **2007**, *250*, 274. (d) Shanbhag, G. V.; Palraj, K.; Halligudi, S. B. *Open Org. Chem. J.* **2008**, *2*, 52. (e) Pandhare, S. L.; Kotbagi, T. V.; Dongare, M. K.; Umbarkar, S. B. *Current Catal.* **2013**, *2*, 62.

(10) (a) Cristau, H. J.; Cellier, P. P.; Spindler, J.-F.; Taillefer, M. *Chem.—Eur. J.* **2004**, *10*, 5607. (b) Taillefer, M.; Xia, N.; Ouali, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 934. (c) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954. (d) Tlili, A.; Monnier, F.; Taillefer, M. *Chem.—Eur. J.* **2010**, *16*, 12299. (e) Racine, E.; Monnier, F.; Vors, J.-P.; Taillefer, M. *Org. Lett.* **2011**, *13*, 2818. (f) Tlili, A.; Monnier, F.; Taillefer, M. *Chem. Commun.* **2012**, *48*, 6408. (g) Danoun, G.; Tlili, A.; Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 12815. (h) Racine, E.; Monnier, F.; Vors, J.-P.; Taillefer, M. *Chem. Commun.* **2013**, *49*, 7412. (i) Lefèvre, G.; Tlili, A.; Taillefer, M.; Adamo, C.; Ciofini, I.; Jutand, A. *Dalton Trans.* **2013**, *42*, 5348.

(11) Ramachary, D. B.; Reddy, Y. V. *Eur. J. Org. Chem.* **2012**, 865.

(12) Refer to the experimental details in the Supporting Information for a precise protocol.

(13) Under optimized conditions (entry 8, Table 1), reactions using secondary acylic amines with phenylacetylene do not afford the desired dieneamine.

DOI: 10.1021/acs.orglett.5b00177
Org. Lett. 2015, 17, 1224−1227